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FUNCTIONAL RESULTS OF CROSSING SENSORY NERVES IN THE RAT

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ONE FIGURE

INTRODUCTION

In the rat the normal innate action phase of limb muscles has been shown to be rigidly predetermined by central coordinating mechanisms in both voluntary and reflex activity. Normal timing of central discharges perseveres without corrective modification after nerve and muscle transplantations which render the original excitation pattern utterly useless, awkward, and detrimental to the animal. In the hind limb, interchanging the nerves of flexor and extensor muscles of the shank or transposing the muscles themselves results in a complete reversal of foot movement that persists permanently despite long training and amputation of other limbs. Likewise in the case of the forelimb, when nerves and muscles involving flexion and extension of the elbow are crossed, the rat is incapable of interchanging the flexor-extensor discharges in the central nervous system so as to correct the peripheral reversal. Special training, limb amputations, and the establishment of other conditions strongly favoring readjustment all fail to bring about the required reintegration, and the brachial muscles continue to contract only in their original uncorrected action phase. Experiment has thus revealed a remarkable lack of plasticity in the organization of the basic motor patterns

[1] This investigation was carried out at the Harvard Biological Laboratories while the author was on appointment as a Zoology Fellow of the National Research Council.

of the rat and also a direct correlation between motor coordination and specific anatomical connections from the motor centers to the musculature (Sperry, '40, '41, '42).

The present experiments were undertaken to find out if the rearrangement of sensory nerve relations in the rat would result likewise in irreparable functional disorder, or whether, by contrast, sensory disturbances may be easily readjusted in the nerve centers. No change in the primary patterns of motor discharge would be required in adaptation to sensory nerve crosses. This and the fact that the central nervous connections are sufficiently elaborate to permit most motor responses to be conditioned to any of a great variety of stimuli might lead one to expect that adjustment should occur without difficulty after crossing sensory nerves. Comparison of the effects of sensory derangement with the aforementioned results of motor derangement should bring further insight into the nature of the basic coordination patterns, particularly with regard to their adaptive plasticity and the functional significance of specific connections between center and periphery.

Although many nerve-cross experiments have been performed on large mixed nerve trunks, attention in the past has been focussed primarily on the results of the motor fiber interchanges and there has been comparatively little recognition of the consequences of distorting the sensory innervation. Apparently the only discussion of the literature available is the rather partial treatment of the subject by Bethe (Bethe and Fischer, '31; Bethe, '31). After crossing the sciatic nerves of a dog from one hind leg to the other in both directions, Bethe ('05; Bethe and Fischer, '31) reported that after regeneration, normal motor coordination was readily restored, but the dog showed false localization of sensation by raising its left leg and turning to the left when the right foot was pinched. The fact that the dog did not correct this false localization failed to weaken Bethe's general conviction ('31, p. 1185) that the nerve centers are capable of extensive and rapid adaptation to rearrangement of sensory nerve connections and that correct localization is restored in animals as

well as in man after exchange of sensory nerve connections. Barron ('34) made anastomoses between the fore and hind limb nerves of the rat such that stimuli applied to the receptive fields of the redistributed nerves in one limb produced reflex movements in the other limb which the nerves had originally supplied. In the cases in which nerve regeneration was most successful, it was reported that reeducation resulted gradually in a complete elimination of the abnormal associated movements until finally even violent stimulation of the reneurotized areas excited responses only in the limb stimulated.

Regeneration of a cutaneous or mixed nerve sutured to its own distal stump, no matter how neat the suture, results inevitably in considerable intermixing of the normal end-organ connections (Langley and Hashimoto, '17; Dogliotti, '35; Kilvington, '41). Reference or false localization of pain, touch, and cold is frequently noticed in the early period of recovery after nerve suture in man, and usually it is said to disappear as the so-called "epicritic" sensibility returns (Trotter and Davies, '09; Head, '20; Stopford, '30). Excitation of misregenerated fibers is assumed by most observers to be the cause of these falsely referred sensations, and their disappearance is commonly attributed to reeducation (Osborne and Kilvington, '09; Boring, '16; Langley and Hashimoto, '17; Lee, '29; Stopford, '30; Lanier et al., '35). Other investigators (Hoffmann, '15; Sharpey-Schafer, '28) have ascribed the phenomenon of reference to the stimulation of outgrowing fibers that have not yet reached their destinations in peripheral localities to which the sensations are referred. According to this view the disappearance of false reference may be a natural consequence of the completion of regeneration. Langley ('08), Hoffmann ('15), and Perthes ('22) each mention an instance, however, in which false localization persisted so long that it probably was due to abnormal sensory connections already established. In none of these latter cases, however, is it stated whether or not correct localization was eventually recovered.

The common assumption that reeducation may spontaneously smooth out functional deficiencies and errors due to aberrant regeneration of sensory nerves in man has been questioned recently by Ford and Woodhall ('38). They point out that tactile localization, two-point sense, and stereognosis never return to even an approximately normal level after nerve regeneration. According to Stopford ('30), reeducation may regularly compensate for interchange of homogeneous nerve fibers, but probably does not correct disturbances resulting from intermixing of heterogeneous fibers, as, for example, when heat, pain, or posture fibers grow out to tactile end-organs. The possibility that several branches of the same sensory neuron may regenerate into widely separated receptor areas, however, confuses the issue of reeducability in all these cases in which a nerve has been sutured back to its own distal stump.

Experiments in which motor adjustment has been reported to follow the cross union of mixed nerves and the transposition of muscles have previously been considered by many workers (Kennedy, '01, '14; Bethe, '05, '31; Osborne and Kilvington, '10; Langley and Hashimoto, '17; Barron, '34; Anokhin, '35) to be evidence of central nervous adjustment to peripheral disarrangement of afferent, particularly proprioceptive, innervation. On the other hand, the slowness of adaptation and its permanent absence under some conditions after muscle transposition in man has been ascribed by Scherb ('27) to antagonism of proprioceptive stimulation. Weiss and Brown ('41) believe that proprioceptive cues from transplanted muscles in man are not of primary importance in retiming the action phase of these muscles.

After the vagus nerve had been led by nerve anastomoses to regenerate into the forelimb, cornea, or tongue of the dog, Anokhin ('35) found that stimulation of these reneurotized regions caused coughing, referred pain reactions, and vomiting. These abnormal responses disappeared gradually after 5 to 10 months and in the case of the forelimb were replaced by normal movements. This recovery of normal reactions was

taken by Anokhin to indicate extensive reintegrative alterations in the functional relations of the sensory vagus nucleus.

Brief mention is made by Ballance ('23) of a human case in which complete recovery of taste sensibility followed union of the central end of the lingual nerve to the distal stump of the hypoglossal nerve.

Regeneration of the completely severed optic nerve of reimplanted and transplanted eyes has been reported to result in restoration of vision in fish, amphibians, and rats,[2] although in the case of rats the validity of the claim has been strongly questioned (Keeler, '29). In urodeles, the regenerative capacity of which is particularly great, complete restoration of visual function is said to follow transplantation and replantation of functional eyes even after the eyes have been rotated 90 or 180 degrees when reimplanted (Stone et al., '37; Stone, '38). After recovery, these amphibians not only show phototactic responses but also follow and snap vigorously at small moving objects. Evaluation of the significance for central nervous function of these striking cases of visual recovery in the lower vertebrates must await more detailed analysis of the visual reactions and also of the new pattern of anatomical connections reestablished between retina and brain centers. In other instances restoration of function after regeneration of sensory nerves to foreign terminals in amphibians has been shown to be due essentially to a developmental rather than a reeducative adjustment (Weiss, '36), and the same may be true of vision.

Inversion of the visual field by the use of glass lenses or reversal of auditory localization with crossed ear phones, though temporary, should be considered because of the similarity in other respects to sensory disturbances produced by surgical translocation. Stratton's earlier report (1897) that the inverted visual field eventually came to look upright under certain conditions was not confirmed by the more extensive experiments of Ewert ('30) who found that the illusory visual disorientation effect did not change noticeably during

[2] For references leading into this literature see Stone and Zaur ('40).

a 14-day period of continuous inversion. Certain types of motor adjustments to the inverted visual field were readily established, however, particularly compensatory movements of the eye and reactions involving overt localizing responses. Young ('28) found that a right-left reversal of auditory localization persisted without correction after pseudophones were worn for 58 hours over a period of 18 days. Some adjustment to the auditory reversal was made, however, by deliberately turning in the opposite direction to that from which sounds seemed to come and by relying on vision rather than on hearing for spatial localization.

Transplantation of a flap of skin with innervation intact may result in erroneous localization just as does the cross union of sensory nerves. Purdy ('34) cites a clinical case in which the terminal phalange of the middle finger was accidentally removed except for some skin of the palmar surface. This residual flap of skin was folded over the cut end of the stump and sutured to the skin on the dorsal surface of the finger. Ten years afterward stimuli applied to the displaced skin were invariably localized in an illusory fashion even on occasions when the subject was permitted to watch the application of the stimulus. Douglas and Lanier ('34) studied a case in which a flap of skin from above the right upper lip was transplanted to the lower lip. Unlike Purdy they state that the initial false localization was soon corrected completely, and they conclude that therefore "local sign" depends mainly on habit formation rather than on innate associations in the central nervous system.

The phantom limb that appears after limb amputation is aroused apparently by proximal irritation of nerve fibers that originally innervated distal segments of the amputated limb. It, therefore, is not unlike illusory sensations resulting from nerve redistribution and skin grafting. In some cases the phantom limb fades out gradually in the course of years; in other cases it persists permanently without change (Gallinek, '39; Riddoch, '41). Disappearance of the phantom is often due to gradual healing and subsidence of irritation of the

severed nerves. Riddoch believes that in some cases it is caused also in part by psycho-physiological inhibition because occasionally a vanished phantom may recur temporarily at times of ill health or emotional disturbances, when central inhibition is subnormal. He mentions, however, that massive painful stimulation at the stump is always able to overcome this adaptive central nervous inhibition of the phantom.

Thus the observations in the literature regarding central nervous adaptability to sensory disarrangements are at present too inconsistent to support any concluding principles. They range from examples of extensive reintegration of reflex associations at the spinal level in lower mammals to permanent incorrigible illusions of sensation at the cortical level in man. Because of the significant implications concerning central nervous function which have already been drawn and may continue to be drawn from this type of data, it is desirable that the entire problem be subjected to further investigation. The present paper is concerned with the capacity of the rat to correct the false localization of sensation and the maladapted spinal reflexes produced by cross union of sensory nerves of the hind feet.

METHOD AND ESSENTIAL CONDITIONS OF THE EXPERIMENTS

The nerves mediating cutaneous and deep sensibility of the left hind foot were crossed into the opposite hind foot. Presumably, as a result of the operation, all sensations aroused by stimulation of the right hind foot would be felt as if they arose in the opposite left foot, and the rat would respond accordingly. This extreme translocation from one foot to the contralateral foot produced a very gross and obvious false localization of sensation. In addition to false localization, it created a manifest maladaptation of simple reflexes at the spinal level, such as extension of the foot against injurious objects instead of withdrawal. The sensory regions supplied by the redistributed nerves included important receptor surfaces, the soles of the feet, which in the course of ordinary activity are subjected to continual stimulation and which thus furnished a

steady flow of sensory cues to facilitate adjustment. The nerves involved in the operation mediate the afferent impulses of definite protective reflexes which are classically familiar. The corrected and original uncorrected forms of the responses concerned, being mutually antagonistic, were easy to distinguish. The crossed nerves were redistributed for the most part to tissues of the same kind as those they originally innervated. This avoided any metabolic depression or alteration of nerve function which might be caused by incompatible or strange tissue relations (see Anokhin, '35; Weiss, '36) or by abnormal over-use or disuse of the redistributed neurons and their centers, effects which might confuse interpretation.

The postoperative conditions made retention of the normal reflex responses decidedly disadvantageous and even injurious to the animals. In arguments directed against the classical reflex conceptions of central nervous integration, Marina ('15), Bethe ('31), Goldstein ('39) and others have contended that restoration of normal function after nerve crossing and muscle transplantation shows that spinal reflex behavior is not the result of rigid central integrating mechanisms as is inferred from the automatism of responses exhibited by decerebrate and spinal preparations. They assert instead that spinal reflex responses as well as the more voluntary reactions are organized centrally on a more plastic dynamic basis according to the instantaneous need and aim of the organism and the adaptiveness of the peripheral effect. Specificity of particular nerve connections between center and periphery as well as between nuclei within the spinal centers is held to be unimportant in the achievement of adequate functional results. An excellent test of this tenet was provided in these intact cerebrate preparations. The normal beneficial effect of the spinal reflexes was reversed to a deleterious effect. According to the above contention, this should result in a rapid dynamic reorganization of the central excitation patterns to suit the new nerve connections.

In the event that an immediate dynamic readjustment on the above basis failed to occur, the preparations served further

as a test of the extent to which the functional disorder might be corrected gradually by adjustments of the learning or "conditioning" type. The fact that the sensory disturbance was grossly obvious and that it was involved inevitably in almost all ordinary activity favored its discovery and correction. The presence of maladapted reactions at lower spinal levels as well as at higher levels of organization made it possible to test the degree to which reeducation might affect different levels of central nervous integration.

The animals were retained and tested for readjustment in various training situations. In this type of recombination experiment it is important to distinguish between reeducative adjustments involving modified use of the recombined parts and adjustments in the remainder of the system that compensate for the non-function or reversed function of the recombined elements. The nature of the functional reversal in this instance made relatively easy the distinction between vicarious function, inhibition, and direct reintegration of the spinal reflexes. Central nervous lesions were used in an attempt to determine the nerve centers involved in the adjustments that occurred.

OPERATION

The operation was performed in three stages. In the first stage the sural, lateral plantar, and medial plantar nerves of the left hind foot were cross united to the distal stumps of the corresponding nerves of the right hind foot. This was done as follows: Through a lateral incision in each leg the right and left sciatic nerves were fully exposed by reflecting the biceps femoris muscles. The sural and plantar branches of the sciatic which innervate the feet were dissected free in both legs. These nerves were cut very low in the shank and foot on the left side and somewhat higher on the right side. In the left leg all other distal branches of the sciatic were cut at convenient points, after which the nerve from the hip to the ankle was freed completely from surrounding tissue. This left sciatic nerve trunk with all its branches was then crossed into the right leg by tunneling it underneath the caudal spinal

column. The central stumps of the left sural, lateral plantar, and medial plantar nerves were then united separately to the distal stumps of the same nerves of the right foot. The nerves were joined by arterial tubulation as described by Weiss ('41 a). The central stumps of the same nerves of the right side were ligated, looped proximally, and inserted into muscle to prevent any regenerating fibers from finding their way back into the foot. The insertions of the reflected muscles were sutured back in position and the incisions were closed with silk thread.

In the second stage operation the saphenous nerve of the left leg was anastomosed to the distal stump of the right saphenous nerve by the following procedure: Through a medial incision in each leg the saphenous nerve was cut very low in the shank of the left leg and as high as possible in the groin of the right leg. The entire length of the central stump on the left side and the upper end of the distal stump on the right side were released from the connective tissue sheath which binds the nerve to its companion artery and vein. The central stump of the left nerve was then crossed over and joined by arterial tubulation to the distal stump of the right nerve. The left nerve was crossed to the right side either by looping it ventrally around the abdomen just under the skin or by sending it directly through the dorsocaudal part of the peritoneal cavity.

The third stage operation consisted merely of pulling out the small remaining uncrossed nerve branches to the right foot. Through a short lateral incision in the lower shank the small peroneal nerves were cut just above the ankle and about a centimeter of the nerves above this point was excised, leaving the right foot neurotized only by nerves that originally had supplied the left foot. No evidence of sensation mediated through a remaining periarterial nerve plexus, as mentioned by Foerster ('30), was observed in these rats.

The first stage operations were performed on young animals ranging in age from 14 to 26 days. Experience with the first few cases indicated that it was better to delay the second and

third stage operations until the nerves previously crossed had regenerated, for otherwise the rats were inclined to chew off the insensitive right foot. Because it was soon found that the completely denervated left foot would usually be chewed off by the rats, it was purposely amputated in later cases in the second stage operation. Although the absence of the left foot was not detrimental to the experiments, being a factor that ought to aid rather than hinder adjustment, a number of additional cases were prepared in which the left foot was preserved by leaving the left saphenous nerve intact instead of crossing it. In these cases about a centimeter of the right saphenous nerve was later excised at the level of the knee.

The main part of all the operations was carried out under a dissecting microscope. A combination of ether and sodium amytal anesthesia was employed. No dressings were applied. Young animals still suckling were isolated for at least 12 hours after the operation to allow any fresh exudate from the incisions to dry thoroughly.

The ultimate effect anatomically of the series of operations was as follows: On the right side, the foot below the ankle and back of the heel was innervated only by crossed nerves that originally had supplied the left foot. The skin above the distal third of the shank and all the deeper structures above the ankle in the right leg retained their normal innervation. On the left side, the foot was amputated at various levels in different cases from just below the ankle to just below the knee. In the left leg cutaneous innervation above the distal third of the shank and innervation of the knee and hip musculature remained normal. Little can be said regarding the details of the fiber connections reestablished within the right foot. Union of the various nerves of the left foot to the same corresponding nerves of the right foot must have resulted in the gross divisions of the right foot being supplied roughly by nerve fibers from the same general region of the left foot. Within the areas supplied by each nerve the connections probably were reestablished largely at random. This is not a serious defect, however, inasmuch as the experiments were

not designed to test discrimination between different points on the same foot, but only discrimination between the right foot as a whole and the left foot.

In those additional cases in which the saphenous nerves were not crossed, the left foot remained intact, innervated only by the saphenous nerve, while the dorsal surface of the right foot was less completely neurotized than in the majority of cases in which the saphenous as well as the medial and lateral plantar and sural nerves were crossed.

When further reference is made to the right and left hind feet, it should be recalled that in all cases it was the right foot which was reinnervated by nerves from the left side.

RECOVERY

Beginning with the fourth week after operation the animals were tested every few days for functional recovery by placing them on a platform which had a floor of cloth netting through which the plantar surface of the foot was easily stimulated. The first signs of recovery appeared on an average of about 48 days after the first operation. Strong mechanical or electrical stimulation of the posterior central region of the sole of the right foot evoked the withdrawal reflex of the left foot but no withdrawal of the right foot. The area from which the crossed responses could be elicited spread gradually during the following 4 to 5 weeks to cover the bottom and lateral side of the foot and toes. Simultaneously the threshold of sensitivity fell gradually until the rats responded to very light touch of the electrodes without electric current. There was a tendency for the pads of the foot to recover before the surrounding skin and for the proximal regions to recover before the more distal. About 60 days after the saphenous nerves had been crossed, cutaneous sensitivity began to reappear in the dorsal surface of the foot.

On completion of nerve regeneration the responses elicited by stimulation of the right foot were completely crossed. When the sole of the right foot was pinched or stimulated electrically, the rat withdrew the left foot. If the stimulation

was prolonged the animal raised the left foot higher and higher by further flexing the left leg and extending the right leg, meanwhile balancing on the stimulator with the right foot (fig. 1, B and C). Occasionally, when lighter stimulation was applied, the left leg was raised and shaken as if to dislodge some object clinging to it. When a wire hook was pulled down lightly over the right toes so as to hold them to the net, the right foot was left in place, but the left leg was jerked upward repeatedly. Whenever the rats responded with the head they always turned to the left side. Frequently they would lick the sole of the left foot or the stump of the left leg while standing on a painful stimulus with the right foot (fig. 1, D). The crossed responses occurred even though the stimulus was applied to the top of the foot from above the net where the rats could see its approach and application. The rats thus responded in all tests as if stimuli applied to the right foot were actually felt in the left foot. This was true whether the left foot was present or had previously been amputated. Nor was there anything in the rats' behavior to indicate that they were in any way aware of the illusory nature of these referred sensations. There was no evidence in these rats of any immediate spontaneous reorganization as described by Marina ('12).

Of twenty-five animals on which the experiments were started, sixteen survived the series of operations and came through the regeneration period with the right leg and foot intact. Two of these cases displayed crossed responses from certain areas of the foot and normal responses from other areas, indicating that fibers from the nerves of the right foot had succeeded in regenerating back into the foot despite precautions taken. The remaining fourteen cases showed complete crossing of responses to stimulation of the right foot as described above. In these cases the borderline between the region from which the responses were all crossed and that from which normal responses were elicitable tended to run around the ankle to the back point of the heel. It was rather variable, however, and in some cases it ran down onto the upper surface of the foot and in others extended up the shank.

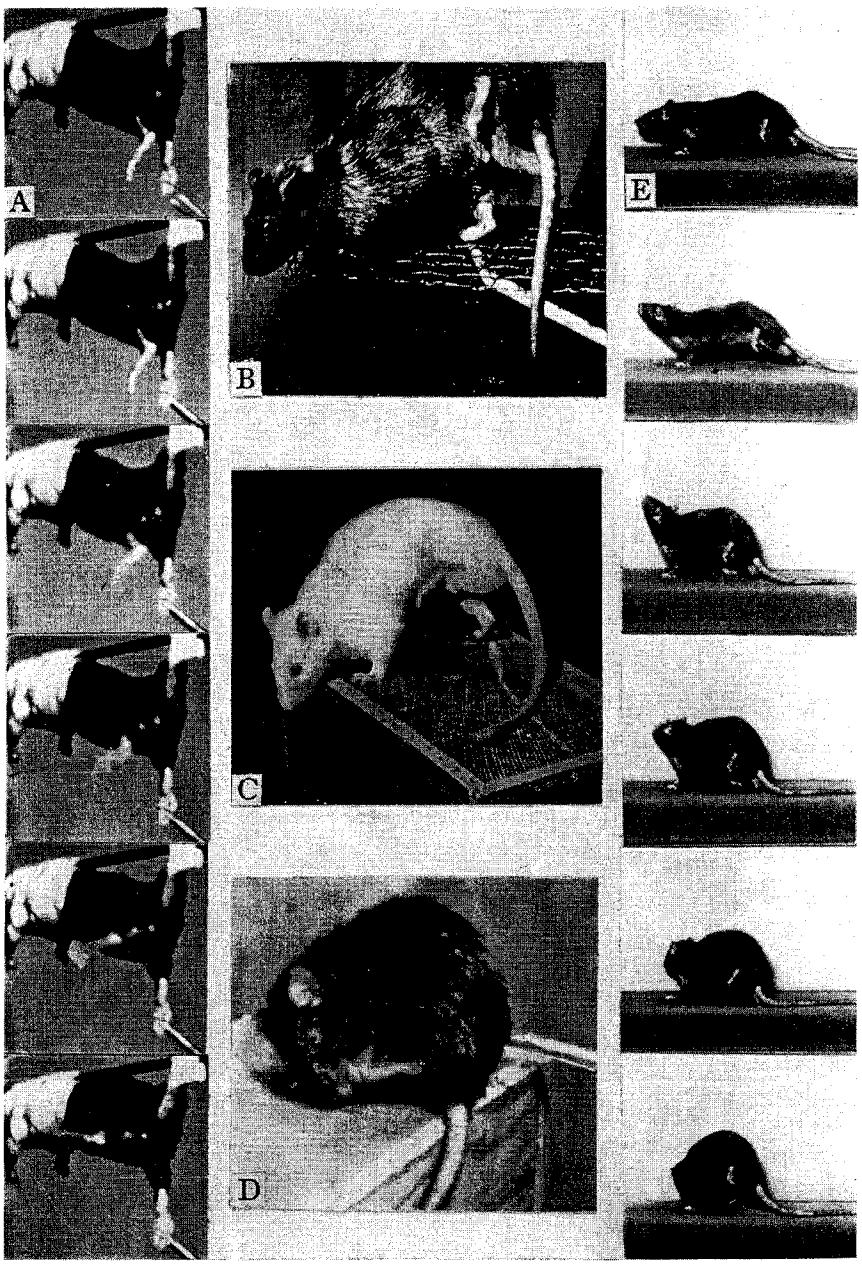

Figure 1

After regeneration was completed, the reneurotized areas were mapped and care was taken throughout the remainder of the experiments to stimulate well within the crossed areas in each case when testing for readjustment.

For convenience in discussing the further history of the sixteen cases, the animals were given individual numbers from 1 to 16 as follows: Numbers 1 through 9 had all nerves of the left foot crossed to the right side as described above, and the left leg was amputated below the knee. Numbers 10 through 14 had the left foot intact innervated by the left saphenous nerve. Numbers 15 and 16 were the cases in which some of the original nerves of the right foot had regenerated back into the foot along with the crossed nerves. The left foot was amputated in number 15 and intact in number 16. Cases number 6 and 7 were albino rats, and the remainder were pigmented.

EFFECT OF EXPERIENCE AND TRAINING

Accidental training. During the recovery period many of the rats broke the insensitive skin of the feet either with their teeth or by abrasion against the wires of their cages. They generally enlarged such lesions by chewing at them. Open "trophic" sores were thus started on the right foot in a number of cases. In four animals (nos. 1, 3, 4, and 10) these

Fig. 1 Enlargements of 16-mm. motion picture film showing rats' reactions to stimulation of right hind foot, the innervation of which is derived entirely from nerves that originally supplied the left hind foot.

(A) Rat strapped to horizontal bar under light anesthesia. When toes of right foot are pinched with forceps, the left instead of the right foot is withdrawn.

(B) Rat on open wire platform. When electric shock is applied to sole of right foot, entire weight of hindquarters is shifted directly onto the stimulator and left foot is lifted high. Ipsilateral extension (right leg) accompanies the crossed flexion (left leg).

(C) Rat on platform of cloth netting. Stimulation and reaction same as in B. Stimulator held against sole of right foot shows as a white line below net.

(D) When a stronger electric shock is applied to right foot, rats turn left and lick left foot. Stimulator, showing as a white streak behind rat, is in contact with dorsal surface of right foot.

(E) When wire clips are pinched into sole of right foot making it painful for the rats to step on this foot, the animals hop about on three legs holding left foot up in the air instead of right, at the same time putting extra weight on the sore foot. Pictures taken 9½ months after operation.

sores lasted well beyond the recovery period and were sufficiently large and painful to cause the animals to walk about on three legs holding one hind leg off the floor. Instead of holding up and protecting the injured right foot, however, these animals raised the healthy left leg and shifted the full weight of the hind quarters directly onto the sore foot (cf. fig. 1, E). Thus excessively aggravated, the ulcers failed to heal normally and persisted at least 6 weeks after the crossed nerves had regenerated in all four cases and as long as 9 weeks in case no. 4. During this time the animals were kept in cages with floors well padded with clean wood shavings. Fresh fruit and vegetables were added to their diet and sulfanilamide powder was frequently dusted into the ulcers.

All four cases continued to walk on the sore right foot. None of them learned to hold up the right leg and shift its weight onto the left. The rats did however learn certain general, non-specific ways of avoiding painful stimulation of the sore foot. For example, when lying down they usually rested in an unnatural position, such that both hind feet were free from pressure. Most often they lay on the right flank and hip with both legs stretched out to the side, the left still being in a more favorable position than the right. It was noticed that the rats licked the sore foot more frequently than the left foot or other parts of the hindquarters. This licking of the sore foot should have been a good method of arousing in the rats an insight to the correct localization of sensations from that foot. In itself, however, it cannot be considered as evidence of corrected localization. Taste and olfaction seemed to be involved primarily, because the rats were observed not infrequently to find and attempt to lick at the lesions of their fellows.

In three of the above four cases, the ulcers eventually healed and these animals thereafter used both hind legs in walking. In no. 10 infection of the original lesion at the base of the third toenail gradually spread along the bones and tendons into the ball of the foot. In spite of frequent draining and application of sulfanilamide, the infection failed to clear up and after

7 weeks the entire foot had become massively swollen and inflamed. Meanwhile the rat continued to hop about on this severely infected foot holding the healthy left foot high in the air. During the eighth week the animal began to squeal frequently when it stepped on the infected foot. After a few steps it would stop and sit on its back licking frantically at its left leg and other parts of the ventral hindquarters. This behavior was intensified until the rat was no longer able to rest. It stopped eating, and died, without learning to stand on the left foot instead of the right.

The training conditions created accidentally in these four animals were probably as good as any that could have been devised experimentally. The incentive for correction of the maladapted reflexes was a natural one and a strong one and was continuously present for a period of at least 6 weeks in all four cases. The contention that the coordination patterns of the spinal system are thoroughly plastic and determined in a purely dynamic manner according to the adaptiveness of the peripheral effect of responses in relation to the well-being or optimal state of equilibrium for the whole animal (Marina, '12; Bethe, '31; Goldstein, '39) is hardly tenable in view of these results.

Special training. It is possible that the increased pain produced by stepping on the right foot in the above cases was not relieved abruptly and completely by raising the foot and that therefore the beneficial effect of the correct response was not as strikingly apparent as it might have been. For this reason further tests of the adjustability of the spinal reflexes were conducted using faradic electrical stimulation which could be released sharply by withdrawal of the foot from the electrodes. In these tests the rats were placed on platforms approximately 20 by 30 cm., through the mesh floor of which electrodes were pushed against the sole of the right foot and held there until the foot was withdrawn. The electrodes were less than 5 mm. apart and the intensity of the stimulus unless otherwise stated was adjusted in each case so that it was just strong enough to cause a definite withdrawal response.

Training was administered in daily half hour periods on an average of 6.5 days per week. During the course of each ½-hour period the foot was stimulated at irregular intervals at least thirty times, giving a minimum of thirty trials per day. At first the rats were rather excitable on the platform, but after a few days became quite accustomed to the training procedure, ceased trying to get off the platform, and behaved calmly.

This training was begun on cases nos. 11, 13, and 15 about 5 weeks after the crossed nerves had recovered function. An attempt was made to eliminate all extraneous stimuli that might aid reeducation other than the electric shock to the foot. The floor of the platform consisted of rather loosely woven cloth stretched very tightly so that it did not give under the weight of the animals, or when the wire electrodes were pushed through it from below. The animals were unable to see the approach of the stimulator through the cloth. When the shock was applied by pressing the sharp electrodes through the cloth against the sole of the foot, there was not enough upward pressure on the foot to stimulate the proprioceptors and sense organs of the joints above the foot which were normally innervated. Had the rats learned to lift the correct foot by relying on visual or other extraneous stimuli mediated through uncrossed nerves it would simply have been another of the many examples of substitutive function comparable on the sensory side to the "trick movements" and vicarious muscle function on the motor side.

When the electric shock was applied to the right foot in the above manner the rats lifted the left leg. The left leg was raised very high by extreme flexion of the hip and knee and also by extension of the right leg. Often the left foot or stump was shaken as if to dislodge an offending object and frequently the rats turned around to the left side and licked the stump or sole of the left foot. Eventually the rats either lost their balance as a result of these reactions or they deliberately hopped away from the original spot so that the right foot was withdrawn from the stimulating electrodes.

The electrodes were always held in place until contact was broken by movement of the right foot after which at least one half minute before reapplication of the stimulus was always allowed for the beneficial effect of the response to register. It was hoped that the animals would come to associate the movement of the right foot with release of the shock and eventually learn to lift the right foot instead of the left when the stimulus was applied. This training was continued for 1 month. After a few days the rats learned to hop away from their initial position more quickly than they had done at first, but there were no signs of a specific correction of the reversed reflexes. They continued to the end to lift the left leg every time the shock was applied and to hop away by pushing down on the electrodes with the right foot. If the shock was very weak they would stand on the electrodes lifting and shaking the left foot. Whenever they turned the head, it was always toward the left side and when the shock was very strong, they continued to lick the left foot or amputated stump instead of the right foot.

Proprioceptive association. After reeducation had failed to occur under the above conditions a platform with slack netting and blunt electrodes was used. When the electrodes were pushed against the foot there was enough slack in the netting so that the hindquarters supported on the right leg could be raised up and down with the electrodes about 1.5 cm. While the rats were standing on the electrodes with the right foot, the left leg raised, they were jolted up and down with the stimulator. This treatment set up kinesthetic stimuli from the upper parts of the right leg in synchrony with the impulses transmitted over the crossed nerves. It was thought that the direct association of normal and crossed stimuli might facilitate adjustment and that the associated normal stimuli might later be gradually eliminated until only those stimuli from cross-innervated areas of the foot were required.

Four cases (nos. 4, 11, 14, and 15) were trained in this way for 28 days. The results were the same as by the previous method. The rats never learned to withdraw the right foot

instead of the left. They did not even learn to inhibit the lifting of the left leg which with the concomitant extension of the right leg only pushed the right foot more strongly against the electrodes. With the slack netting this extension of the right leg and the shifting of the weight of the hindquarters onto the right side decidedly increased the severity of the electric shock.

Visual association. Following this procedure, another method was tried using an open wire platform with meshes 1.5 cm. square through which the rats could easily see the approach and application of the electrodes. To enhance the visual cues a tuft of white cotton about 2 cm. in diameter was impaled on the end of the stimulator. The foot was approached slowly and stimulated from above as well as from below. At intervals the right front foot was also shocked to attract the rat's attention to the stimulator. The rats frequently followed and bit at the stimulator. When their attention was thus attracted, the electrodes were moved slowly back from the right front foot to the right hind foot. As soon as the right foot was shocked, however, the rats always withdrew the left foot, and if the shock was strong, they turned completely about to the left side. Cases nos. 11, 13, and 15 were trained in this way on the open wire platform for 24 days. As in the previous training series there was no sign of inhibition or correction of the maladaptive spinal reflexes.

Combined visual, tactile, and kinesthetic association. In a final attempt to train the rats to withdraw the correct foot, a platform was constructed with a floor of slack open netting with meshes 6 mm. square. All the means of facilitating adjustment with extraneous cues used in the previous procedures were combined. In addition the right foot was frequently approached by running the cotton-tufted electrodes down over the fur of the knee and shank of the right leg until the electrodes came to the foot where they were pressed against the skin innervated by crossed nerves. In this way the rats could be made to turn first to the correct side when the hair of the right upper leg and shank was rubbed in approaching the right

foot. As soon as the electrodes hit the area innervated by crossed nerves, even though the electrodes were directly in front of the rat's eyes and in contact with his vibrissae, the animals lifted the left leg instead of the right and turned about to the opposite side. For 39 days, cases nos. 4, 13, and 16 were trained by this final method in which visual, tactile, proprioceptive, and other kinesthetic stimuli were associated with the electric shock. No evidence of any improvement of the reversed responses had appeared at the end of this period, 9 months after operation. The attempt to induce an adaptive reorganization of the innate spinal reflexes was thereupon abandoned.

Localization tested by conditioned responses. It seemed possible that the animals in the course of the above training had become aware of the fact that it was actually the right foot and not the left which was receiving the electric shock, but that the spinal reflexes were too rapid, powerful, and automatic to be controlled by "voluntary" activity from the higher centers. Thus, if permitted to make a voluntary movement to a relatively neutral warning stimulus preceding the shock itself, the rats might know enough to lift the correct foot. This was tested as follows: Eight cases (nos. 1, 3, 7, 9, 11, 13, 14, 15) were conditioned to withdraw the fore limbs, left hind limb, or tail when the stimulator without any electric potential was touched to these parts. This conditioning was readily established by touching the electrodes to various points on the forefeet, left hind foot, and tail and, after a moment's contact, turning on the electricity. The rats soon learned to withdraw the limbs and tail rapidly before the shock was administered. They had generalized this warning contact of the stimulator to other parts of the body, because when it was touched to different points on the trunk, they jumped away before the current was switched on. When the animals had thus been trained to withdraw quickly from the neutral warning stimulus, the stimulator was touched to the sole of the right foot. When this was done, in all eight cases the left leg was immediately withdrawn, and the right foot was extended

against the stimulator where it was shocked as the electric current came on.

In addition a somewhat similar test was applied to four of the cases (nos. 4, 7, 11, 14). A warning buzzer was sounded and then an electric shock applied to the right foot. It was found that normal rats soon learn to lift the right foot at the warning signal before the shock is applied. When this training procedure was undertaken with the experimental cases, it was quite clear in three of the rats that the first few conditioned withdrawal responses were made with the left leg instead of the right. In the fourth case, no. 4, the results were not significant because the rat had a short stump on the left side and from the beginning used the right foot to help move the entire body away from the spot where it was resting before the stimulator was applied. Once established, the conditioned withdrawal of the left leg could be reinforced by withholding the shock to the right foot or extinguished by continuing to apply the shock, but this is of no consequence to the problems of the present experiments. The main point to be noted is that the rats, 9 months after operation and after all the training to which they had been subjected, voluntarily withdrew the left leg instead of the right to the neutral warning signals in these two tests. This voluntary withdrawal of the leg must be distinguished clearly from the reflex withdrawal produced by nociceptive stimulation of the right foot. The results indicate that the rats had not become sufficiently aware of the erroneous nature of stimuli mediated by the crossed nerves to correct even these voluntary reactions, much less the automatic spinal reflexes.

Localization of wire clips. Rats will normally remove offending objects such as thorns, pieces of tape, wire clips, burrs, etc. from the skin and fur. Seven of the experimental cases (nos. 4, 7, 9, 11, 13, 14, 15) were tested to see if they could learn to locate and remove wire clips pinched into the skin of the right foot. The wire clips were made from pieces of copper wire about 8 mm. in length bent in a U shape. With forceps the two ends of the clip were pinched tightly into the

sole of the right foot, making it painful to the rats to step on this foot. It was not difficult to pinch the clips in place because the rats made no effort to withdraw the right foot but pulled away the left foot instead. With the clip thus implanted, the rats were released in a large cage, the floor of which was well padded with wood shavings. The first 3 days on which this was tried the rats walked about on three legs, holding the left leg off the floor (fig. 1, E). They frequently turned and licked the left foot or stump, but generally failed to locate the wire clip during the hour period in which they were watched. In a number of instances the clips were found still in place on the right foot 24 hours later.

On the fourth day pieces of white cotton string, 4 cm. long, were tied to the clips with the ends left free. With this visual aid most of the rats succeeded in finding and removing the clips within the hour training period. Thereafter the clips were always placed in random order on various parts of the body including the right foot. In the early stage of training the rats kept turning frequently to lick the left foot or stump and it was only by chance that they happened to notice the string dangling from the right foot, usually when they used this foot to scratch themselves. With further training erroneous trials became less frequent and the rats began to turn more deliberately to the right side. As they became more proficient, the string tied to the clips was gradually shortened until it was unnecessary to use this visual sign at all. By the end of 3 weeks, with approximately 100 trials on the average, all but one of the rats had learned to locate and remove the clips from the sole of the right foot. Improvement with further training was negligible. Their efficiency varied greatly on different trials. At times they turned to the right foot and pulled out the clip in less than $\frac{1}{2}$ minute after it was put on. On other occasions the clip was not removed in less than 10 minutes, depending in large part apparently upon the painfulness of the clip. The rats continued to the end to make occasional false starts by turning partly toward the left leg. The animals were not relying on visual cues because removal

of both eyes in five cases did not affect their proficiency. Olfactory stimuli were not involved because the performance was not impaired when the metal clips were washed thoroughly and implanted with clean forceps. Care was taken to vary the procedure when planting the clips so that no consistent cues were available from this source. The learned performance seemed to be dependent primarily upon the stimuli aroused by the pricking and pinching of the clips transmitted over the crossed nerves. Number 7, which failed to show any improvement with training, continued to turn to the left stump instead of the right foot. The clips usually remained on the foot until they were rubbed off in walking. Occasionally no. 7 found and pulled them off, but these accidental successes did not lead to further improvement. Placing the clips on the foot with less pressure or putting on two or three of them until the rat squealed with each step as it hopped on the extended right foot both failed to educe any improvement. This rat was just as proficient as the others on those intermediate trials in which the clips were placed on the right leg above the foot and on other parts of the body.

Learning to locate clips on the right foot did not result in any correction of the maladaptive spinal reflexes. To the end all of the rats continued to shift extra weight onto the painful clips in the right foot and hold the left leg high in the air. In removing the clips they usually sat or lay down and stretched the right leg forward, approaching it by bending the head underneath the body ventrally. Pulling at the clips with their teeth in this position produced spasmodic withdrawal reflexes of the left leg. This resulted not infrequently in the animal's turning away from the clips in the right foot to lick the left foot or stump. The rats often turned to lick the left foot or stump for a few moments after removing the clips from the right foot. When they approached the right foot laterally instead of ventrally, they balanced on the extended right leg and continued, in the very act of searching for and removing the clips from the right foot, to hold up the left leg as high as it would go. As a result they commonly lost their balance and

fell from this contorted position. Although the rats used the left leg regularly for support when the right foot was not irritated by the metal clips, they never learned to shift their weight onto the left leg and hold up the right foot either to eliminate the pain of stepping on the clips or to facilitate their removal.

The persistence of occasional false starts toward the left leg and the fact that the rats frequently turned to lick the left foot after pulling at the clips on the right foot indicated that the clips still felt as if they were on the left foot although the rats had learned that they were actually to be removed from the right foot. The quick voluntary withdrawal of the foot to a neutral stimulus as tested above was again tested in these six cases after they had learned to locate clips on the right foot. The results were the same as before; the rats withdrew the left instead of the right foot.

Cortical lesions were made in four of the above cases in an attempt to destroy the learned performance. The lesions were made in the area mediating placing and hopping reactions in the rat and which according to Brooks ('33) probably contains the cortical sensory representation of the limbs. Extensive bilateral lesions in this area abolished placing reactions, but did not completely eradicate the capacity to localize clips pinched on the right foot. The lesions produced a noticeable deterioration of the habit, but not to the pre-training level.

Before the cortical lesions were inflicted, the areas of the redistributed nerves were remapped in all the experimental cases. Little difference from the first delineation of the crossed areas was observed. In several cases where the dorsal surface of the toes had been relatively insensitive, sensitivity, mediated by the crossed nerves, had definitely increased. There was no indication that uncrossed fibers had entered the region of the redistributed nerves except in the two cases (nos. 15, 16) already mentioned. The eleven experimental cases still living (nos. 1, 3, 4, 6, 7, 9, 11, 13, 14, 15, 16) were sacrificed a little over 11 months after operation. On postmortem dissection, the right and left sciatic nerve trunks lying side by side in the

right leg were found to be easily separable with no sign of fibers intercrossing between them. In two cases (nos. 9, 12) a fine nerve strand from the right peroneal nerve could be traced as far as the dorsolateral surface of the ankle. In no. 1, the left saphenous nerve had failed to regenerate into the stump of the right saphenous, apparently because the arterial junction had pulled loose. A very fine strand of fibers from the right side had entered the upper end of the degenerated right stump. In cases nos. 15 and 16, a substantial strand of fibers from the right tibial nerve was found joining the left tibial nerve, accounting for the functional mixture already observed. No other evidence of unintended regeneration was discovered.

DISCUSSION

Persistence of the normal hind limb reflex patterns without any central readjustment to suit the revised peripheral innervation under the conditions of these experiments discloses an extreme stability in their organization. Not only motor patterns, as shown previously, but associations of complete reflex circuits from the sensory to motor side remained strongly fixed in these rats. No evidence of that prodigious adaptation capacity claimed for the spinal centers on the basis of former experiments of this sort (Osborne and Kilvington, '10; Marina, '15; Bethe, '31; Anokhin and Iwanow, '36; and others) has appeared in our results, either in the form of immediate spontaneous reorganization or in adjustments of the learning and "conditioning" type. Contrary to the contention that spinal excitation patterns are dynamically regulated in an equipotential nerve network and hence thoroughly plastic, these experiments support the view that reflex coordination is directly dependent upon a stable specificity of interneuron relations which is largely inherited rather than acquired and which remains highly refractory to rearrangement through experience.

This innate organization of the spinal cord which remains fixed is of course sufficiently intricate in design to permit considerable transitory variation in coordination patterns such as

appears regularly in the general activity of the rat. Such moment-to-moment variation, however, involves no permanent readjustments of the innate organization of the spinal system. Moreover, the patterning of this evanescent elasticity of coordination, adaptive when anatomical relations are normal, is achieved through and depends upon the basic structural design and is therefore definitely limited by it. When specific relations of the innate structure itself are rearranged as in our present and previous nerve-cross and muscle-transposition experiments, the capacity for immediate adaptation of the central patterns proves to be insufficient and a corresponding disturbance of function follows.

Such functional disorder may be partially corrected in an indirect manner by simple inhibition of the function of the rearranged elements, or by compensating variations in the function of other parts of the system which still retain their normal innate relations, or by corrective modifications in cortical control over the spinal patterns involved. Accordingly one would expect in ascending the vertebrate scale to find the possibilities for corrective adjustment to increase with increasing differentiation of the basic spinal coordination patterns and also with increasing differentiation and elaboration of cortical influence over the spinal system. Whether the reeducative adjustments following disarrangements of the normal sensori-neuro-muscular relations observed in primates ever involve reorganization of the basic innate relations of the spinal system itself, rather than this indirect type of correction, remains uncertain.

The above interpretation emphasizing the existence of a stable specificity of interneuron organization rather than a homogeneous equipotentiality of the spinal centers is in accordance with the data on spinal coordination in amphibians (Weiss, '41 b) and also with the classical reflex studies on decerebrate and spinal mammals (Sherrington, '06). The basic specificity of spinal organization may be determined primarily by anatomical relations as conceived by Sherring-

ton and his co-workers ('32) or by resonance phenomena as proposed by Weiss ('28, '36).

That the rats learned to locate clips placed in the area of the redistributed nerves is not surprising since this performance consisted of "voluntary" activity mediated through the higher brain centers and did not demand reintegration of the hind limb reflexes. The motor coordination patterns involved were not novel but had been present from the beginning. Learning thus consisted merely of selecting from among readily available reactions those with a beneficial effect. The original reflex patterns of the spinal system, although extremely disadvantageous with the altered peripheral relations, remained uncorrected or even inhibited.

The immediate sensory impressions of localization as well as the spinal reflexes apparently remained unmodified in the course of this learning, because the animals continued to make incidental false starts to the left side and to lick the left foot when the clips on the right foot became especially irritating. The rats behaved as if the clips were felt on the left foot, even though they had learned that the clips were actually to be found on the right foot. Also in later tests of other voluntary reactions to stimulation of the right foot the rats responded as though the left foot had been stimulated. The training had not resulted in any general and stable reorganization of the inherent central schema of localization such that voluntary reactions were automatically governed by the new reference scheme. This apparent persistence of the original sensory impression may be compared to the prolonged illusion of stimuli from a phantom limb in human patients despite the patient's knowledge that no limb is present. Afferent integration, as thus indicated, appears to be quite stable up to and including at least the primary relations in the sensory cortex. The results strongly suggest that the basis of cutaneous "local sign" in the rat, at least, is largely innate rather than acquired.

It cannot be stated for certain on the basis of these results that the structural organization of the rat's central nervous system absolutely precludes reeducative correction of those

central reflex patterns involved in our experiments, since some method of training yet untried might prove successful. Unmodifiability of the original spinal patterns under the above conditions, however, does present strong additional evidence for the existence in the cord of a definite specificity of interneuron organization which is highly stable.

SUMMARY

1. In ten rats the sural, saphenous, medial plantar and lateral plantar nerves of the left hind foot were crossed to the distal stumps of the corresponding nerves of the right hind foot and the left hind foot was amputated. In six rats the left sural and plantar nerves were crossed to the corresponding nerves of the right foot and the left hind foot was left intact innervated only by the uncrossed saphenous nerve. The remaining uncrossed nerves to the right foot were excised in all cases.

2. Reinnervation of the right hind foot by nerves that originally had supplied the left hind foot produced in all sixteen cases a false localization of sensation and a decidedly maladaptive reversal of hind limb reflexes.

3. Despite prolonged training under various conditions, the maladaptive spinal reflexes remained in every case wholly uncorrected or even inhibited by central nervous adjustment.

4. Six of seven cases so tested learned to locate and remove wire clips pinched on the right hind foot. Localized bilateral cortical lesions in the sensori-motor area of the hind limbs failed to cause deterioration of the habit to its pre-training level. This learned performance consisting of "voluntary" reactions involving the higher brain centers is to be distinguished from the hind limb reflexes which continued automatically $10\frac{1}{2}$ months after operation to respond in reverse while the rats were in the act of removing the wire clips from the correct foot.

5. The experiments furnish evidence of pronounced stability in spinal reflex organization in the rat.

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